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08/338,282

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EXAMINER	
GAMBEL, P	
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DATE MAILED: 12/27/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 9/20/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-5, 32, 34-36 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☑ Claims 6-31, 33, 37-63 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-5, 32, 34-36 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Claims 6-31, 33 and 37-63 have been previously canceled.
Claims 1, 32 and 34 have been amended.
Claims 1-5, 32 and 34-36 are pending.

16. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 16. Applicant will submit formal drawings upon the indication of allowable subject matter.

17. The disclosure is objected to because of the following informality:

The use of the trademark "SEPHAROSE" has been noted in this application. It should be capitalized or accompanied by the ™ symbol wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required.

18. Upon reconsideration of applicant's arguments/amendment and a review of the art on the relative broad success of α4β1-specific antibodies in various animal models, the previous rejection of claims 1-5, 32 and 34-36 under 35 U.S.C. § 112, first paragraph, has been withdrawn. Treating with α4β1-specific antibodies does not appear to be subject to the same species- and model-dependency as other cell surface markers including other adhesion molecules. VLA-4-specific antibodies have been shown to block α4-dependent adhesion in vitro and have shown beneficial effects in vivo in seven different species and in a wide variety of organ systems (see Lobb, J.Clin. Invest., 1994; The Pathophysiolgic Role of α4 Integrins In Vivo, particularly the Summary).

19. Upon reconsideration of the art which indicates that the MEL-14 specificity is homologous to L-selectin rather than α4, the previous rejections under 35 U.S.C. § 102(e) as being anticipated by Butcher (U.S. Patent No. 5,403,919) and under 35 U.S.C. § 103 as being unpatentable over Butcher (U.S. Patent No. 5,403,919) in view of Hemler et al. (EP 0 330506) and Takada et al. (Nature, 1987) have been withdrawn.

Carlos et al. disclose that L-selectin is the human homologue of the murine peripheral lymph node homing receptor that was originally identified by the monoclonal antibody MEL-14 (Blood, 1994; see page 2070, column 2, paragraph 4).

NEW REJECTION BASED UPON APPLICANT'S AMENDMENT

20. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 32 and 34-36 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed: "other than those lining high endothelial venules (HEV)", as the specificity of the claimed methods relying upon $\alpha 4\beta 1$-specific antibodies.

The amendment filed 9/20/95 in Paper No. 33 is objected to under 35 U.S.C. § 132 because it introduces new matter into the specification. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "other than those lining high endothelial venules (HEV)".

Applicant's amendment, filed 9/20/95 (Paper No. 33), indicates that support for this amendment is inherent in the application as a whole and refers to several sections of the instant specification, as filed. According to applicant, the application is specifically directed to lymphocyte adhesion to endothelium that has been activated by inflammatory cytokines (page 45, lines 22-32), as exemplified by large vessel endothelium (page 45, lines 22-32; page 46, lines 9-15).

Contrary to applicant's allegations, the negative limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

The instant invention is drawn to methods of inhibiting the interaction of α4β1 with its ligands leading to the intervention of the migration of lymphocytes through the vascular endothelium into tissues (see Summary of the Invention). Here, it is disclosed that the present invention, therefore has particular clinical utility in the suppression of the immune response; in various specific embodiments of the invention, the adherence of lymphocytes to endothelium may be inhibited systemically, or may, alternatively, be localized to particular tissues or circumscribed areas. Nowhere in the specification, as filed, is there teaching or description that would guide one skilled in the art to select and/or recognize that the specificity of the instant α4β1-specific antibodies inhibit lymphocyte adherence to endothelial cells at the exclusion of HEV. Contrary to applicant's arguments, the instant disclosure, as filed, is drawn to inhibiting lymphocyte adherence to endothelial cells or to preventing lymphocyte migration into tissues by preventing lymphocyte adhesion to endothelial cells in a number of circumstances and not limited to the exclusion of HEV. The specification does not describe nor enable identification of this negative limitation.

Applicant is required to cancel the new matter, drawn to "other than those lining high endothelial venules (HEV)", in the response to this Office action.

NEW GROUNDS OF REJECTION

21. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman,* 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. The following double patenting rejection is based upon different inventions since the instant claims currently are a species of the genus encompassed by the claims of copending application USSN 08/477,777. However, applicant is reminded that the instant limitation of endothelial cells "other than those lining high endothelial venules (HEV)", as the specificity of the claimed methods relying upon $\alpha 4\beta 1$-specific antibodies is considered new matter and should be canceled.

Claims 1-5, 32 and 34-36 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 32 and 34-36 copending application Serial No. 08/477,777. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current amended claims reading on endothelial cells "other than those lining high endothelial venules (HEV)" would be a species of the genus encompassed by the methods of inhibiting lymphocyte-endothelial adherence or lymphocyte migration with $\alpha 4\beta 1$-specific antibodies.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

23. The following statutory double patenting rejection is provided to indicate the appropriate rejection when the negative limitation is canceled from the instant claims.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-5, 32 and 34-36 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-5, 32 , and 34-36 of copending application Serial No. 08/477,777. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

25. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

26. Upon reconsideration of the prior art, the following New Grounds of Rejections are set forth presently. It is noted that while endothelial cells "other than those lining high endothelial venules (HEV)" would provide a limitation that is free of the prior art; this negative limitation is considered new matter as set forth above. Therefore, the following rejections under 35 U.S.C. § 102(a) and 35 U.S.C. § 103 are made in the context of that this negative limitation will be canceled. Therefore the claims are drawn broadly to inhibiting lymphocyte adhesion to endothelial cells. In addition, claims 1-5 are drawn to both in vitro and in vivo methods while claims 32 and 34-36 are drawn to in vivo methods.

27. Claims 1-3 are rejected under 35 U.S.C. § 102(a) as being anticipated over Holzmann et al. (Immunol. Rev., 1989; see entire document, particularly Figure 2). Holzmann et al. teach that the VLA-4α-specific antibody P4C2 inhibiting lymphocyte binding to Peyer's patch high endothelial venules, therefore the inhibition of lymphocyte-endothelial adherence by an α4β1-specific antibody is meant by the reference. This is the same P4C2 antibody recited in the claims. Applicant is reminded that nothing more is required of the reference than the substance of the claims.

28. Claims 1-5, 32 and 34-36 are rejected under 35 U.S.C. § 103 as being unpatentable over Holzmann et al. (Immunol. Rev., 1989) and Holzmann et al. (Cell, 1989) and in view of Butcher (U.S. Patent No. 5,403,919), Hemler et al. (EP 0 330506) and Takada et al. (Nature, 1987). Claims 1-5, 32, 34-36 are drawn to treating to methods of inhibiting leukocyte-endothelial adherence and leukocyte migration with α4β1-specific antibodies.

It is noted that the claimed α4β1 specificity reflects two components, that is, an α4 component and a β1 component. Further, each component has been known to associate with different members of either the α or β family. Therefore, antibodies that bind α4 will bind α4β1 and antibodies that bind β1 will bind α4β1. Also, α4β1 goes by VLA-4 as well.

Holzmann (Immunol. Rev.) reviews the role of adhesion molecules in lymphocyte circulation and migration and sets forth the family as determined by their respective α and β subunits (see Introduction). Holzmann teaches the α subunit-specific antibody anti-LPAM-1 which can inhibit lymphocyte adhesion to Peyer's Patch HEV (pages 47-50). The structure of LPAM-1 is virtually identical to the α chain of the human VLA-4 (α4β1) (pages 50-51) and LPAM-2 is analogous the human VLA-4 (pages 56-57). In addition, the β1 subunit is common to the human fibronectin receptor and VLA proteins (page 52, paragraph 3). Further, α4-specific antibodies including the instant P4C2 antibody are able to inhibit human leukocyte-endothelial adhesion (page 55 including Figure 2). This reference differs from the instant claims by not exemplifying in vivo methods and applying β1-specific antibodies as anti-adhesion reagents.

Similarly, Holzmann (Cell) teaches the α subunit-specific antibody anti-LPAM-1 which can inhibit lymphocyte adhesion to Peyer's Patch HEV and that the structure of LPAM-1 is virtually identical to that of the human VLA-4 (α4β1) (see entire document). In the Introduction, the inhibition of lymphocyte-endothelial interactions and of lymphocyte adherence/migration by integrin-specific antibodies including the β1-specificity is taught. In addition to the interaction with extracellular matrix proteins, VLA-4 is taught to be a cell-cell adhesion molecule,

page 43, column 2, paragraph 2). Holzmann et al. also teach that species differ in these homing receptors (page 44, column 1, paragraph 1). Holzmann et al. differs from the instant claims by not exemplifying the inhibition of human VLA-4-endothelial interactions with α4β1-specific antibodies.

Both Holzmann et al. references cite the MEL-14 antibody in defining and applying anti-adhesive antibodies in leukocyte-endothelial interactions. Butcher teach methods to control leukocyte extravasation by inhibiting leukocyte-endothelial interactions with adhesion molecule-specific antibodies (see entire document, particularly columns 1-8). Butcher teaches the in vivo inhibition leukocyte-endothelial interactions and leukocyte extravasation by the MEL-14 monoclonal antibody (see column 2, particularly, lines 2-7 and 35-65). Butcher teaches the methods of screening for inhibitory antibodies for adhesion-mediated events, which are essentially the same in vitro models exemplified by Holzmann et al. above.

In teaching the importance of α4β1 (VLA-4) in addition to α4 alone as involved in leukocyte adhesion during inflammation, Hemler et al. reviews the structure of VLA antigens including the association of distinct α subunits with a common β subunit (see entire document). Hemler et al. teaches that VLA proteins can interfere with cell attachment mechanism and inhibit cell binding to matrix or cell connective proteins and, in turn, inhibit tumor cell metastasis and interfere with immune cell function (page 5, paragraph 4). Hemler et al. teaches the importance of the VLA antigens, including VLA-4 in various inflammatory conditions (page 5, paragraph 4). Although, Hemler et al. disclose blocking by adhesion molecules proteins, Holzmann et al. and Butcher teaches that adhesion molecule-specific antibodies also can block adhesion-mediated events.

In teaching the importance of the β1 specificity in leukocyte adhesion, Takada et al. exemplifies VLA β-specific antibodies can block cell adhesion to matrix proteins (see entire document, particularly page 607, column 2, paragraph 1).

It is noted that the cited references do not disclose the claimed P4C2 (α4-specific) is taught by Holzmann et al. (Immunol. Rev.), while the P4C10 (β1-specific) antibody is not disclosed. Therefore, the α4-specific antibodies taught by Holzmann et al. and Hemler et al. and the β1-specific antibodies taught by Holzmann et al., Takada et al. and Hemler et al. appear to be functionally equivalent to the instant claimed specificities. In addition, such α4-specific and β1-specific antibodies would have generated by the ordinary artisan applying routine monoclonal antibody technology in association with the adhesion blocking screening assays as taught by Holzmann et al. and Butcher et al.

to select for the appropriate anti-adhesion antibodies. It is the burden of the applicant to show the unobvious difference between the claimed invention and those that are generated or could be produced by the referenced methods.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of inhibiting leukocyte-endothelial adhesion and leukocyte extravasation, as taught by Holzmann et al. with α4β1-specific (α4-specific or β1-specific) antibodies as anti-adhesive agents in the determination of lymphocyte-endothelial interactions as well in design of therapeutic agents to treat inflammatory reactions associated with these interactions. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

29. Even though New Grounds of Rejections have been set forth above, the examiner will address applicant's arguments, filed 9/20/95 (Paper No. 33), as they apply to the previous rejections. Applicant is reminded that the current rejections are made in the context that the new matter, drawn to endothelial cells "other than those lining high endothelial venules (HEV)" will be canceled as new matter. Also, the Holzmann references are now the primary references in the rejections made under 35 U.S.C. § 102(a) and 35 U.S.C. § 103.

Upon a review of the art, it is noted that MEL-14 appears to be analogous to L-selectin and not VLA-4, however Butcher is no longer the primary reference therefore applicant's arguments are rendered moot on this point. It is noted that Butcher and the teachings related to MEL-14 have been applied as secondary references due to the similarity of this system to VLA-4 and lymphocyte-endothelial interactions as cited by the current primary references by Holzmann et al.

Although applicant argues that Hemler and Takada are drawn to the function of VLA-4 with extracellular matrix proteins, the Holzmann et al. references teach the blocking of lymphocytes to HEV with α4-specific antibodies as well as the role of both α4-specific β1-specific events in lymphocyte-endothelial interactions and blocking these events by antibodies.

Although, applicant's arguments against Holzmann et al. are based upon the distinction of HEV taught by Holzmann et al. versus the negative limitation amended by applicant. Although this distinction is convincing for the amended limitation, this is not found convincing for the instant application because this negative limitation must be canceled because it is new matter. In the absence of the amended negative limitation, the combined teachings with the Holzmann et al. references as the primary references render the instant claims in the absence of the recitation of endothelial cells "other than those lining high endothelial venules (HEV)" as a limitation.

30. No claim allowed.

31. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4065 or (703) 305-7939.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Margaret Parr can be reached on (703) 308-2454. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
December 26, 1995